In re Application of: Yoseph SHAALTIEL et al.
Serial No.: 10/554,387
Filed: October 25, 2005
Restriction Office Action Mailing Date: April 7, 2008

Examiner: Delia M. RAMIREZ
Group Art Unit: 1652
Attorney Docket: 30570

In the Claims:

1-72. (Cancelled)

73. (Previously Presented) An isolated nucleic acid sequence encoding a human lysosomal protein being contiguously linked to a C-terminal vacuolar targeting signal and an N-terminal endoplasmic reticulum signal peptide.

74. (Previously Presented) An isolated nucleic acid sequence encoding a human lysosomal protein being contiguously linked to a C-terminal endoplasmic reticulum retention signal and an N-terminal endoplasmic reticulum signal peptide.

75. (Previously Presented) The isolated nucleic acid sequence of claim 73, wherein wherein said human lysosomal protein is a glucocerebrosidase.

76. (Previously Presented) The isolated nucleic acid sequence of claim 73, wherein said human lysosomal protein is a human α-galactosidase.

77. (Previously Presented) The isolated nucleic acid sequence of claim 74, wherein said human lysosomal protein is a human glucocerebrosidase.

78. (Previously Presented) The isolated nucleic acid sequence of claim 74, wherein said human lysosomal protein is a human α-galactosidase.

79. (Previously Presented) The isolated nucleic acid of claim 73, wherein said vacuolar targeting signal is a basic tobacco chitinase A gene vacuolar targeting signal.

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80. (Previously Presented) The isolated nucleic acid of claim 79, wherein said vacuolar targeting signal is as set forth in SEQ ID NO: 2.

81. (Previously Presented) The isolated nucleic acid of claim 73, wherein said endoplasmic reticulum signal peptide is as set forth in SEQ ID NO: 1.

82. (Previously Presented) The isolated nucleic acid of claim 73, wherein said human lysosomal protein comprises an amino acid sequence as set forth in SEQ ID NO: 8.

83. (Previously Presented) The isolated nucleic acid of claim 73, wherein said nucleic acid sequence is as set forth in SEQ ID NO: 7.

84. (Previously Presented) The isolated nucleic acid of claim 73, wherein said nucleic acid sequence is as set forth in SEQ ID NO: 13.

85. (Previously Presented) The isolated nucleic acid of claim 73, further comprising a promoter functional in plant cells transcriptionally linked to said nucleic acid sequence.

86. (Previously Presented) The isolated nucleic acid of claim 85, wherein said promoter sequence is a Cauliflower Mosaic Virus S-35 promoter sequence.

87. (Previously Presented) The isolated nucleic acid of claim 73, further comprising a transcriptionally linked terminator sequence functional in plant cells.

88. (Previously Presented) The isolated nucleic acid of claim 73, wherein said isolated nucleic acid sequence optionally further comprises additional operably linked control, promoting and regulatory elements and/or selectable markers.

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89. (Previously Presented) The isolated nucleic acid of claim 88, wherein said terminator is an octopine synthase terminator of *Agrobacterium tumefaciens*, and the regulatory element is the TMV (Tobacco Mosaic Virus) omega translational enhancer element.

90. (Previously Presented) A nucleic acid construct capable of expression in a plant cell comprising the isolated nucleic acid of claim 73.

91. (Previously presented) A cell comprising the nucleic acid construct of claim 90.

92. (Previously Presented) The cell of claim 91, recombinantly producing said human lysosomal enzyme.

93. (Previously Presented) The cell of claim 92, wherein said human lysosomal protein is recombinantly produced so as to have at least one xylose and at least one exposed mannose residue.

94. (Previously Presented) The cell of claim 91, wherein said cell is a plant cell.

95. (Previously Presented) The cell of claim 94, wherein said plant cell is a plant root cell selected from the group consisting of *Agrobacterium rihzogenes* transformed root cell, celery cell, ginger cell, horseradish cell and carrot cell.

96. (Previously Presented) The cell of claim 95, wherein said plant cell is a carrot cell.

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97. (Previously Presented) The cell of claim 91, wherein said cell is an *Agrobacterium tumefaciens* cell.

98. (Previously Presented) A human lysosomal protein comprising at least one xylose residue and at least one exposed mannose residue.

99. (Previously Presented) A human lysosomal protein comprising at least one exposed mannose residue and at least one fucose residue having an alpha (1-3) glycosidic bond.

100. (Previously Presented) The human lysosomal protein of claim 98, further comprising at least one fucose residue having an alpha (1-3) glycosidic bond.

101. (Previously Presented) The human lysosomal protein of claim 99, further comprising at least one xylose residue.

102. (Previously Presented) The human lysosomal protein of claim 98, wherein said lysosomal enzyme is a glucocerebrosidase.

103. (Previously Presented) The human lysosomal protein of claim 98, wherein said lysosomal enzyme is an α-galactosidase.

104. (Previously Presented) The human lysosomal protein of claim 98, wherein said human lysosomal protein is contiguously linked to a C-terminal vacuolar targeting signal.

105. (Previously Presented) The human lysosomal protein of claim 98, wherein said human lysosomal protein is contiguously linked to a C-terminal vacuolar targeting signal and an N-terminal endoplasmic reticulum signal peptide.

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106. (Previously Presented) The human lysosomal protein of claim 105, wherein said vacuolar targeting signal is a basic tobacco chitinase A gene vacuolar targeting signal.

107. (Previously Presented) The human lysosomal protein of claim 106, wherein said vacuolar targeting signal is as set forth in SEQ ID NO: 2.

108. (Previously Presented) The human lysosomal protein of claim 105, wherein said endoplasmic reticulum signal peptide is as set forth in SEQ ID NO: 1.

109. (Previously Presented) The human lysosomal protein of claim 102, wherein said human glucocerebrosidase comprises an amino acid sequence as set forth in SEQ ID NO: 8.

110. (Previously Presented) The human lysosomal protein of claim 98, wherein said lysosomal protein having a biological activity.

111. (Previously Presented) The human lysosomal protein of claim 98, wherein said biological activity is uptake into macrophages.

112. (Previously Presented) The human lysosomal protein of claim 98, wherein said biological activity is enzymatic activity.

113. (Previously Presented) The lysosomal protein of claim 111, having an increased affinity for said macrophages, in comparison with the corresponding affinity of a naturally occurring lysosomal protein to said macrophages.

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114. (Previously Presented) A pharmaceutical composition comprising the human lysosomal protein of claim 99 and a pharmaceutically acceptable carrier.

115. (Previously Presented) A plant cell preparation comprising a human lysosomal protein comprising at least one xylose residue and at least one exposed mannose residue.

116. (Previously Presented) A plant cell preparation comprising a human lysosomal protein comprising at least one exposed mannose residue and at least one fucose residue having an alpha (1-3) glycosidic bond.

117. (Previously Presented) The plant cell preparation of claim 115, further comprising at least one fucose residue having an alpha (1-3) glycosidic bond.

118. (Previously Presented) The plant cell preparation of claim 116, further comprising at least one xylose residue.

119. (Previously Presented) The plant cell preparation of claims 115, wherein said lysosomal protein is a human glucocerebrosidase.

120. Previously Presented) The plant cell preparation of claim 115, wherein said human lysosomal protein comprises an amino acid sequence as set forth in SEQ ID NO: 8.

121. (Previously Presented) The plant cell preparation of claim 115, wherein said lysosomal protein is a human α-galactosidase.

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122. (Previously Presented) The plant cell preparation of claim 115, wherein said human lysosomal protein is contiguously linked to a C-terminal vacuolar targeting signal

123. (Previously Presented) The plant cell preparation of claim 115, wherein said human lysosomal protein is contiguously linked to a C-terminal vacuolar targeting signal and an N-terminal endoplasmic reticulum signal peptide.

124. (Previously Presented) The plant cell preparation of claim 122, wherein said vacuolar targeting signal is a basic tobacco chitinase A gene vacuolar targeting signal.

125. (Previously Presented) The plant cell preparation of claim 122, wherein said vacuolar targeting signal is as set forth in SEQ ID NO: 2.

126. (Previously Presented) The plant cell preparation of claim 123, wherein said endoplasmic reticulum signal peptide is as set forth in SEQ ID NO: 1.

127. (Previously Presented) The plant cell preparation of claim 115, wherein said human lysosomal protein having at least one exposed mannose residue comprises a dominant fraction of said lysosomal protein, as measured by linkage analysis.

128. (Previously Presented) A pharmaceutical composition comprising the plant cell preparation of claim 115 and a pharmaceutically acceptable carrier.

129. (Previously Presented) A method of producing a lysosomal protein comprising:

preparing a culture of recombinant cells transformed or transfected with the nucleic acid construct of claim 90; and

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culturing said cell culture under conditions permitting the expression of said protein, wherein said protein produced by said cells comprises at least one xylose residue.

130. (Previously Presented) The method of claim 129, wherein said cell culture is cultured in suspension.

131. (Previously Presented) The method of claim 129, further comprising:
purifying said protein.

132. (Previously Presented) The method according to claim 129, wherein said protein produced by said cell has at least one xylose and at least one exposed mannose residue.

133. (Previously Presented) The method according to claim 131, wherein said lysosomal protein binds to a mannose receptor on a macrophage.

134. (Previously Presented) The method according to claim 129, wherein said lysosomal protein has increased affinity for said macrophage, in comparison with the corresponding affinity of a naturally occurring lysosomal protein to said macrophage.

135. (Previously Presented) Use of a biologically active lysosomal enzyme as defined by claim 110, in the manufacture of a medicament for the treatment or prevention of a lysosomal storage disease.

136. (Previously Presented) The use of claim 135, wherein said lysosomal enzyme has increased affinity for macrophage cells, in comparison with the

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corresponding affinity of a naturally occurring lysosomal enzyme to said macrophage cells.

137. (Previously Presented) The use according to claim 135, wherein said disease is Gaucher's disease.

138. (Previously Presented) A method for treating a subject having lysosomal storage disease using a biologically active recombinant lysosomal enzyme, comprising:

(a) providing a recombinant biologically active lysosomal enzyme as defined in claim 110; and

(b) administering a therapeutically effective amount of said recombinant biologically active lysosomal enzyme to said subject.

139. (Previously Presented) The method according to claim 138, wherein said lysosomal enzyme is glucocerebrosidase (GCD).

140. (Previously Presented) The method according to claim 138, wherein said lysosomal storage disease is Gaucher's disease.

141. (Previously Presented) The method according to claim 138, wherein said target cell at the target site is a Kupffer cell in the liver of said subject.

142. (New) A human lysosomal protein comprising a human glucocerebrosidase which comprises an amino acid sequence as set forth in SEQ ID NO: 8 contiguously linked to a C-terminal vacuolar targeting signal as set forth in SEQ ID NO: 2 and an N-terminal endoplasmic reticulum signal peptide as set forth in SEQ ID NO: 1.

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143. (New) The human lysosomal protein of claim 142, which comprises an amino acid sequence as set forth in SEQ ID NO: 14.

144. (New) A pharmaceutical composition comprising the human lysosomal protein of claim 142 and a pharmaceutically acceptable carrier.